Food Intake and Body Weight: Regulation by Apo A-IV in the Brain

Dr. Patrick Tso

Dr. Patrick Tso is Professor of Pathology, Associate Director of the Cincinnati Obesity Research Center, and Director of the Center for Lipid and Atherosclerosis Research at the University of Cincinnati College of Medicine. Additionally, he is the Director of the Cincinnati Mouse Metabolic Phenotyping Center, funded by NIDDK. Dr Tso is a highly respected researcher in the area of lipid (fat) metabolism, a field in which he has worked for over 20 years. At the September 2008 meeting of the NIDDK Advisory Council, Dr. Tso shared insights from his exciting research on how food intake and body weight are regulated by apolipoprotein A-IV (apo A-IV). The following are highlights of his presentation.

Feeling Full after a High-Fat Meal: The Discovery That Apo A-IV Regulates Food Intake

How does a high-fat meal make one feel full? Dr. Tso described his laboratory's research to understand what causes satiety and the insights that have emerged from these studies about the role of a small biologic factor called apo A-IV, which is made in humans and animals. Intrigued by the dramatic increase in intestinal apo A-IV production known to occur after ingestion of dietary fat, Dr. Tso and one of his post-doctoral fellows, Dr. Kazuma Fujimoto, investigated a potential role for apo A-IV in satiety. The researchers conducted their experiments in rodents, and began with a focus on a body fluid called lymph, which varies in composition depending upon what food has been ingested. After a fatty meal, lymph from the abdomen contains an abundance of apo A-IV along with fat absorbed from the food. To assess whether this fluid might curtail food intake, they compared different samples of lymph, some with fat and some without. After administering the lymph samples intravenously into fasting rats, they assessed how much the rats subsequently ate. In describing this study, Dr. Tso shared an anecdote about the experimental design. He recounted that Dr. Fujimoto was concerned that the rats might be too "worried" to eat if a person was nearby. So, Dr. Fujimoto decided to speak to each rat for 15 minutes every day (in his native Japanese) to help the animals feel comfortable around him. This procedure evidently worked, as the rats did eat—but those who had been given the fat-containing lymph ate significantly less. Thus, something in the lymph was signaling that a relatively small meal would be sufficient. The researchers then investigated which component of the lymph might be causing this satiety effect: the fat, or the apo A-IV. After a series of additional experiments, they discovered that it was apo A-IV.

Site of Action: The Brain

Dr. Tso next sought to discover where in the body apo A-IV exerts its effect to reduce food intake. Although apo A-IV was originally found to be produced in the intestine, substantial regulation of appetite occurs in the brain. Thus, Dr. Tso, with another post-doctoral fellow, Dr. Koji Fukagawa, explored whether apo A-IV could reduce food intake when infused directly into the brain. The answer was yes, as determined by further studies in rats.

Building on this research, Dr. Tso and another of his post-doctoral fellows, Dr. Min Liu, found that apo A-IV is not only produced in the intestine, but it is also synthesized in a part of the brain, the hypothalamus, known to play a crucial role in the control of food intake and body weight. In further experiments in rats, they demonstrated that excess apo A-IV in the brain,

from infusions, reduces body weight in parallel to its effect on satiety.

From Feeding to Fullness: Elucidating Biologic Pathways in the Brain

Having illuminated the role of brain apo A-IV in regulating food intake, Dr. Tso and his colleagues next asked: What regulates apo A-IV? They first tested whether brain apo A-IV, like apo A-IV in the intestine, is affected by feeding and fasting. From studies in rats, the researchers found that apo A-IV levels in the brain substantially decreased after fasting, a result that is consistent with their findings regarding the role of apo A-IV in satiety; an animal that had not eaten for a day should not feel full. The researchers next explored the effects of different types of food on apo A-IV levels in the brain. When the rats, after fasting, were given their standard "chow," apo A-IV levels in the brain did not change significantly. If the animals instead ate high-fat food, their brain apo A-IV levels greatly increased.

Dr. Tso and his laboratory also discovered that apo A-IV levels in the brain fluctuate with the circadian rhythm—the day/night cycles. Levels of this satiety-inducing factor were lowest at night, when rats typically eat, and peaked during the day, when rats normally do not eat. Thus, the daily rise and fall of apo A-IV levels mirrored the animals' feeding patterns. The researchers then explored whether the changes in apo A-IV levels were caused by the cycles of light and dark per se, or by the concomitant cycles of feeding and fasting. When they shifted the rats' meal times to the daylight hours (by providing food only during the day), the researchers found that apo A-IV levels changed, too. Dr. Tso concluded that it was the cycles of feeding and fasting that affected apo A-IV levels, rather than daylight and darkness. That is, under normal conditions, apo A-IV levels are low at night (when food is typically available), and the rats are thus able to eat. Their ingestion of food causes apo A-IV levels to rise by the morning hours, which in turn makes the rats too full to eat during the day. After not eating for a while, the apo A-IV levels fall again so that by night time, the rats become hungry and eat.

To further explore the pathway by which apo A-IV causes satiety, Dr. Tso and his research team investigated whether apo A-IV interacts with the hormone leptin. Mice deficient in leptin are strikingly obese, and this hormone also plays a critical role in body weight regulation in humans. The researchers measured apo A-IV levels, and the effects of fasting and feeding, in normal mice and mice that lacked leptin (as a result of a genetic mutation). In the leptin-deficient mice, levels of apo A-IV in the brain were lower than in the normal mice. Additionally, when leptin-deficient mice were given a high-fat meal, the levels of brain apo A-IV did not increase as in normal mice. The scientists then injected leptin into the deficient mice, and found that this led to a restoration of normal levels of apo A-IV. From these and other experiments, the researchers concluded that leptin regulates apo A-IV, and that leptin and apo A-IV interact to reduce food intake and body weight.

Dr. Tso's research team then turned their attention to other factors in the brain known to regulate food intake, collectively referred to as the melanocortin system, to determine whether these factors interact with apo A-IV. Again using rodents as a model system, the researchers found that apo A-IV and a major component of the melanocortin system, called POMC, are present in the same brain cells, and both apo A-IV and POMC levels are low during fasting. Administering apo A-IV led to an elevation in POMC levels as well. This research, together with additional studies, demonstrated that apo A-IV also interacts with the melanocortin system to inhibit food intake.

Conclusions—Apo A-IV

Dr. Tso's research on apo A-IV has yielded novel insights into the regulation of food intake and satiety. In concluding his presentation, Dr. Tso noted that apo A-IV has other functions as well, related to fat metabolism and other biologic processes. By

shedding light on the regulation of satiety, this research will also advance understanding of what could go awry in obesity, with implications for potential intervention approaches.

Dr. Tso acknowledged the contributions of the scientists who worked with him on these studies when they were post-doctoral fellows in his laboratory: Drs. Kazuma Fujimoto, Koji Fukagawa, and Min Liu. Additionally, Dr. Tso thanked his long-time collaborator on this research, Dr. Stephen Woods, who is also a Professor at the University of Cincinnati.